Improving Stratification for Children With Late Bone Marrow B-Cell Acute Lymphoblastic Leukemia Relapses With Refined Response Classification and Integration of Genetics

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Abstract: PURPOSE Minimal residual disease (MRD) helps to accurately assess when children with late bone marrow relapses of B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) will benefit from allogeneic hematopoietic stem-cell transplantation (allo-HSCT). More detailed dissection of MRD response heterogeneity and the specific genetic aberrations could improve current practice. PATIENTS AND METHODS MRD was assessed after induction treatment and at different times during relapse treatment until allo-HSCT (indicated in poor responders to induction; MRD 10^{-3}) for patients being treated for late BCP-ALL bone marrow relapses (n = 413; median follow-up, 9.4 years) in the ALL-REZ BFM 2002 trial/registry (ClinicalTrials.gov identifier: NCT00114348). RESULTS Patients with both good (MRD $< 10^{-3}$) and poor responses to induction treatment reached excellent event-free survival (EFS; 72% v 65%) and overall survival (OS; 82% v 74%). Patients with MRD of 10^{-2} or greater after induction had reduced EFS (56%), and their MRD persisted until allo-HSCT more frequently than it did in patients with MRD of 10^{-3} or greater to less than 10^{-2} (P = .037). Patients with 25% or more leukemic blasts after induction (early nonresponders) had the poorest prognosis (EFS, 22%). Interestingly, patients with MRD of 10^{-3} or greater before allo-HSCT (late nonresponders) still had an EFS of 50% and OS of 63%, which in principle justifies allo-HSCT in these patients. From a panel of selected candidate genes, TP53 alterations (frequency, 8%) were the only genetic alteration with independent prognostic value in any MRD-based response subgroup. CONCLUSION After induction treatment, MRD-based treatment stratification resulted in excellent survival in patients with late relapsed BCP-ALL. Prognosis could be further improved in very poor responders by intensifying treatment directly after induction. TP53 alterations can be defined as a novel genetic high-risk marker in all MRD response groups in late relapsed BCP-ALL. Here we identified early and late nonresponders to be considered as events in future trials.

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original reports

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abstract

PURPOSE Minimal residual disease (MRD) helps to accurately assess when children with late bone marrow relapses of B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) will benefit from allogeneic hematopoietic stem-cell transplantation (allo-HSCT). More detailed dissection of MRD response heterogeneity and the specific genetic aberrations could improve current practice.

PATIENTS AND METHODS MRD was assessed after induction treatment and at different times during relapse treatment until allo-HSCT (indicated in poor responders to induction; MRD $\geq 10^{-3}$) for patients being treated for late BCP-ALL bone marrow relapses (n = 413; median follow-up, 9.4 years) in the ALL-REZ BFM 2002 trial/registry (ClinicalTrials.gov identifier: NCT00114348).

RESULTS Patients with both good (MRD $< 10^{-3}$) and poor responses to induction treatment reached excellent event-free survival (EFS; 72% *v* 65%) and overall survival (OS; 82% *v* 74%). Patients with MRD of 10^{-2} or greater after induction had reduced EFS (56%), and their MRD persisted until allo-HSCT more frequently than it did in patients with MRD of 10^{-3} or greater to less than 10^{-2} ($P = .037$). Patients with 25% or more leukemic blasts after induction (early nonresponders) had the poorest prognosis (EFS, 22%). Interestingly, patients with MRD of 10^{-3} or greater before allo-HSCT (late nonresponders) still had an EFS of 50% and OS of 63%, which in principle justifies allo-HSCT in these patients. From a panel of selected candidate genes, *TP53* alterations (frequency, 8%) were the only genetic alteration with independent prognostic value in any MRD-based response subgroup.

CONCLUSION After induction treatment, MRD-based treatment stratification resulted in excellent survival in patients with late relapsed BCP-ALL. Prognosis could be further improved in very poor responders by intensifying treatment directly after induction. *TP53* alterations can be defined as a novel genetic high-risk marker in all MRD response groups in late relapsed BCP-ALL. Here we identified early and late nonresponders to be considered as events in future trials.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Contemporary intensive combination chemotherapy and the risk-adapted indication for allogeneic hematopoietic stem-cell transplantation (allo-HSCT) has brought event-free survival (EFS) and overall survival (OS) to approximately 50% and 60%, respectively, for children and adolescents with relapsed acute lymphoblastic leukemia (ALL).[1-3] Time to relapse is the strongest predictor of outcome and is used in most protocols for risk stratification at relapse in combination with immunophenotype and relapse site.[1-6] Patients with late relapses of B-cell precursor ALL (BCP-ALL) and bone marrow involvement have intermediate risk. Patients with early combined or isolated extramedullary BCP-ALL relapses are also classified as intermediate risk because they achieve better EFS than patients with very early or early isolated bone marrow relapses. The ALL-REZ BFM P95/96 trial identified minimal residual disease (MRD) after induction treatment as the strongest prognostic factor for intermediate-risk relapsed ALL.[7] MRD of less than 10^{-3} after induction predicted 10-year EFS greater than 70% and supported the continuation of consolidation and maintenance chemotherapy, whereas MRD of 10^{-3} or greater predicted 10-year EFS of less than 20% with conventional intensive combination

chemotherapy alone.[7-9] Therefore, an MRD-based strategy to intensify treatment with allo-HSCT after consolidation therapy in patients with intermediate-risk relapses and MRD of 10^{-3} or greater after induction was implemented in the ALL-REZ BFM 2002 (ClinicalTrials.gov identifier: NCT00114348) trial and substantially improved outcome (8-year EFS, 64% *v* 18% in the historical control) in patients with MRD-based poor response.[9] However, patients with early intermediate-risk relapses had poor prognoses even if they responded well to induction (MRD $< 10^{-3}$), and were recommended to receive allo-HSCT.[9] The impact of response heterogeneity, kinetics, and genetic variation of patients in the ALL-REZ BFM 2002 trial was not addressed in the early report.

Here we provide more detailed subgroup analyses for patients with late bone marrow relapses uniformly treated according to the ALL-REZ BFM 2002 protocol with data from a substantially extended patient cohort and doubled follow-up time.[9] Our central question was whether the current stratification strategy is adequate for all subgroups of patients with late BCP-ALL relapses or whether there are patient subgroups for whom treatment strategies should be

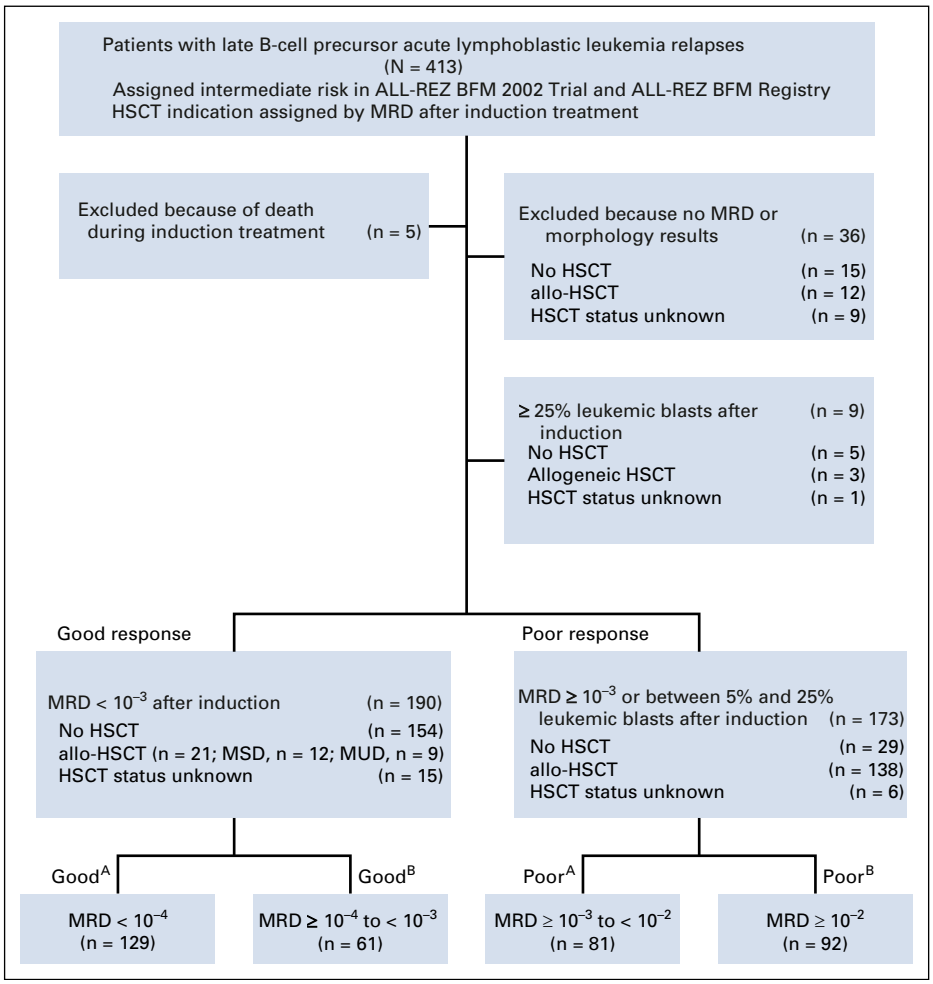

FIG 1. CONSORT diagram of patients with late B-cell precursor acute lymphoblastic leukemia bone marrow relapses for minimal residual disease (MRD) after induction treatment, allogeneic hematopoietic stem-cell transplantation (allo-HSCT) indication according to trial protocol, and allo-HSCT history. MRD-based response to induction was applied in the ALL-REZ BFM 2002 trial and the ALL-REZ BFM Registry protocol for patient stratification to therapy intensification with allo-HSCT. Of the 190 patients with MRD good response, a small proportion of patients (11%; 21 of 185 with available data) received an allo-HSCT, and allo-HSCT from matched sibling donor was allowed (12 of 21); however, allo-HSCT from a matched unrelated donor (MUD; 9 of 21) was not recommended. Of the 173 patients with an indication for allo-HSCT, 17% (29 of 167) did not undergo an allo-HSCT. Reasons for not undergoing allo-HSCT in the 29 patients were patients or guardians refused the treatment (n = 5), no suitable donor was found (n = 7), an event occurred before reaching allo-HSCT (n = 13), pretreatment toxicity burden prevented transplantation (n = 3), and treatment was continued in another country (n = 1).

changed in future trials. The prognostic relevance of different MRD levels after induction treatment and MRD kinetics between induction at relapse and allo-HSCT in second clinical remission (CR2) were investigated in addition to the prognostic relevance of genetic subgroups determined from a panel of selected candidate genes.

PATIENTS AND METHODS

This study included children and adolescents (median age, 9.7 years at relapse diagnosis; interquartile range, 7.1 to 14.2 years; maximum, 25.7 years; patients age 18 years or older, n = 30) with late bone marrow BCP-ALL relapses diagnosed between January 1, 2002, and December 31, 2015. Late bone marrow relapse was defined as disease recurrence with or without extramedullary involvement, diagnosed 6 months or more after completing first-line treatment or 30 months or more from initial diagnosis (Data Supplement).

Study participants were treated according to the intermediate-risk group arm of the ALL-REZ BFM 2002 trial and the subsequent the ALL-REZ BFM registry (since October 2012). Trials were approved by the local ethics committees and informed consent was given by patients and/or guardians before enrollment and treatment. Patients with MRD of 10^{-3} or greater after induction at relapse were

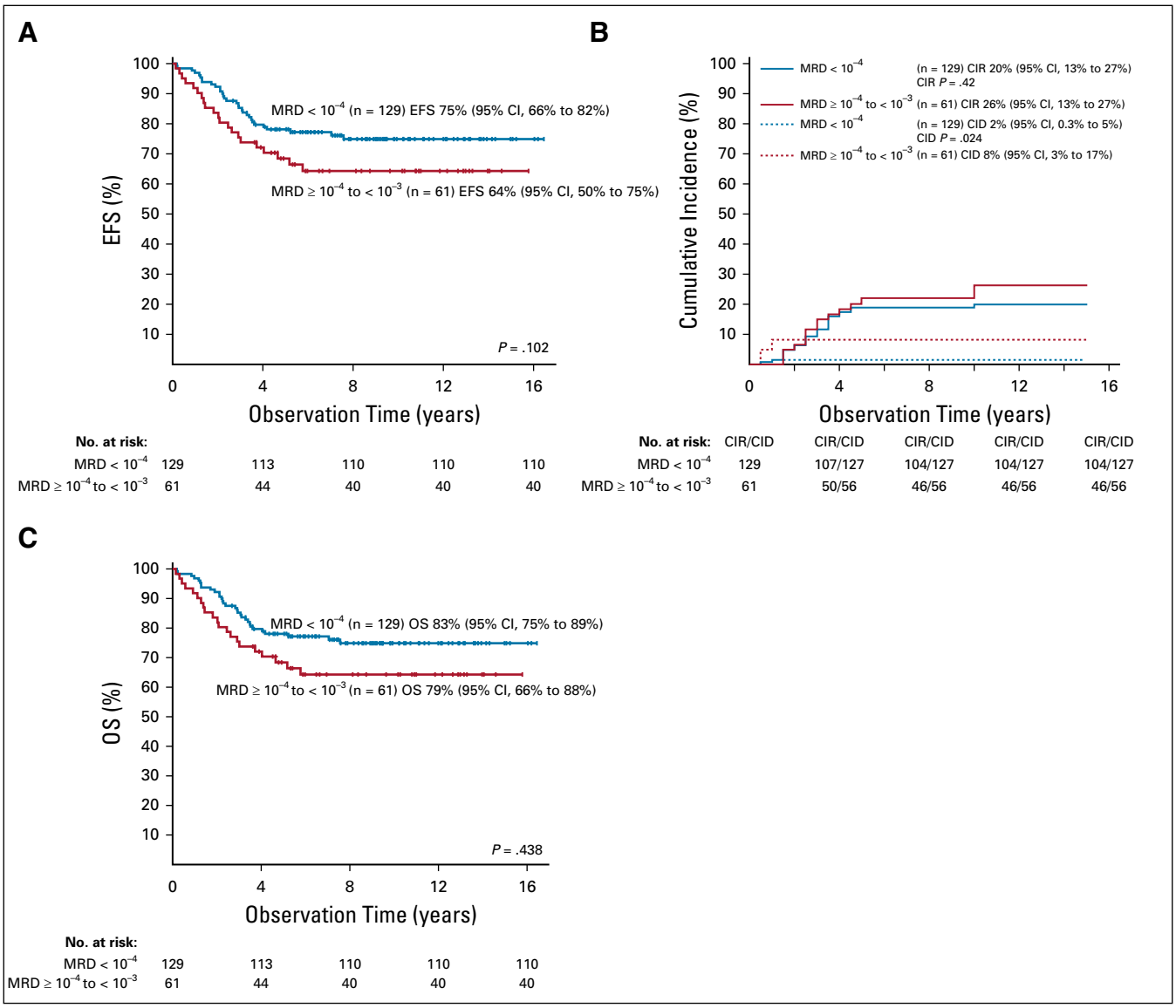

FIG 2. Survival differs between two subgroups of good responders to induction. (A) Kaplan-Meier analysis estimating the event-free survival (EFS) at 10 years in patients who responded well to induction treatment. (B) Competing risk analysis of cumulative incidence of subsequent relapses (CIR) and cumulative incidence of treatment-related deaths (CID) at 10 years in patients who responded well to induction. (C) Kaplan-Meier analysis estimating the 10-year overall survival (OS) in patients who responded well to induction. Minimal residual disease (MRD) in bone marrow was used to more finely divide good response into two groups (MRD $< 10^{-4}$ and MRD $\geq 10^{-4}$ to $< 10^{-3}$) after induction.

recommended for allo-HSCT in CR2 from a matched sibling or matched unrelated donor (≥ 9 of 10 identical *HLA* alleles). Patients with MRD of less than 10^{-3} continued to receive consolidation and maintenance chemotherapy, but allo-HSCT from a matched sibling donor was also permitted. Most patients receiving allo-HSCT were enrolled into the ALL-SCT 2003 and ALL-SCT BFM international trials.[10]

Multiple bone marrow samples were collected between relapse diagnosis and allo-HSCT (Data Supplement), of which the analyses presented here primarily compare samples collected after induction treatment and 30 days or fewer before allo-HSCT. MRD was assessed by real-time quantitative polymerase chain reaction (PCR) using T-cell receptor or immunoglobulin gene rearrangements as described previously.[9,11] Data were analyzed according to the EuroMRD Consortium guidelines.[12] Real-time PCR and/or fluorescence in situ hybridization (FISH) were used to detect gene fusions or translocations common in pediatric ALL, including *ETV6-RUNX1*, *TCF3-PBX1*, *BCR-ABL1*, *MLL-AFF1*, and *MLL-MLLT1*. High-hyperdiploidy and hypodiploidy were flow cytometrically identified by DNA index and/or multiplex ligation-dependent probe amplification (SALSA multiplex ligation dependent probe amplification [MLPA] P181 Centromere probe mix; MRC Holland, Amsterdam, the Netherlands). Copy number alterations in *EBF1*, *IKZF1*, *CDKN2A*, *CDKN2B*, *PAX5*, *ETV6*, *BTG1*, *RB1*, and the *PAR1* region were detected by using the SALSA MLPA P335 ALL-*IKZF1* probe mix (MRC Holland). The resulting *P2RY8-CRLF2* fusion was validated by reverse transcription PCR for *PAR1* deletions. *TP53* deletions were detected by using the SALSA MLPA P056 probe mix and were confirmed by FISH. Mutations in key *TP53*, *KRAS*, *NRAS*, and *FLT3* exons were identified by Sanger sequencing.[13-15]

Distributions of clinical and genetic variables among different MRD subgroups were compared by χ^2 or Fisher's exact test for categorical variables and by Mann-Whitney *U* or Kruskal-Wallis tests for continuous variables. EFS and OS were analyzed by using Kaplan-Meier analysis and a two-tailed log-rank test. Cumulative incidence of competing risks, cumulative incidence of subsequent relapse (CIR), and cumulative incidence of therapy-related death (CID) were assessed by using the Kalbfleisch-Prentice method and Gray statistics. Multivariable Cox regression included variables considered to be relevant for outcome or associated with MRD response to induction treatment for 30 days or fewer before allo-HSCT in stepwise forward testing. Models were compared by using the log likelihood-ratio

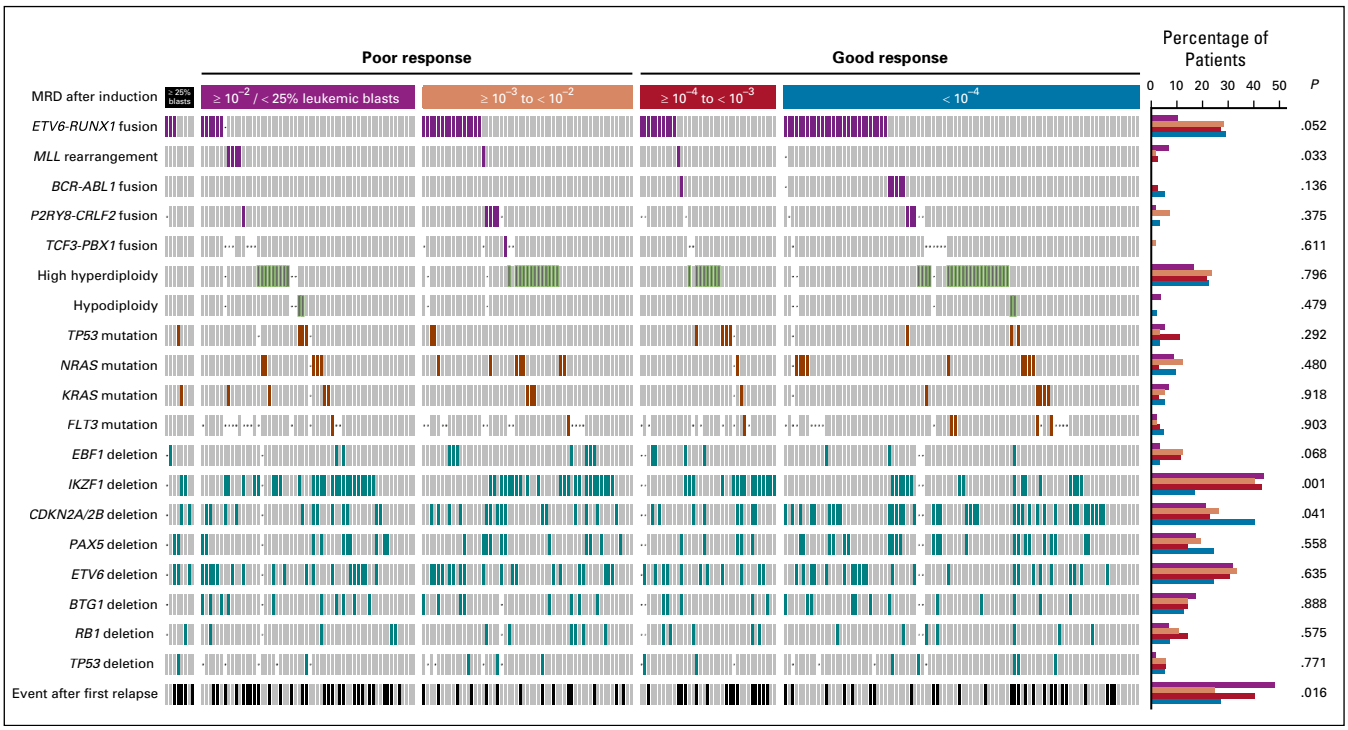

FIG 3. Patterns of genetic alterations in the bone marrow relapse are heterogeneous among different response subgroups. The oncoplot visually compares genetic alterations detected in the bone marrow relapse.[25,26] Relapse genomics are sorted according to minimal residual disease (MRD)–based response in patients to induction treatment. Response to induction was divided into the five finer subdivisions detected in survival analysis: early nonresponse (≥ 25% leukemic blasts), poor^B (< 25% leukemic blasts but MRD ≥ 10^{-2}), poor^A (MRD ≥ 10^{-3} to < 10^{-2}), good^B (MRD ≥ 10^{-4} to < 10^{-3}), and good^A (MRD < 10^{-4}). Color denotes the presence of recurrent fusion genes (purple), high hyperdiploidy or hypodiploidy (olive), mutations (brown), gene deletions (turquoise), subsequent event (black), or no data (black dots).

TABLE 1. Clinical and Genetic Parameters and Their Association With Outcome

Parameters	EFS at 10 Years						
	Total No. of Patients	EFS, %	95% CI	*P**	HR	95% CI	*P***
Sex				.75			
Male	199	68.7	62 to 75		1.00		
Female	164	67.5	60 to 74		1.06	0.73 to 1.50	.75
Quartiles for age at diagnosis of relapse, years				.25			
< 7.1	98	71.0	61 to 79		1.00		
≥ 7.1 to < 9.7	84	72.5	61 to 81		0.87	0.50 to 1.53	.64
≥ 9.7 to < 14.2	92	70.5	60 to 79		1.03	0.61 to 1.74	.90
≥ 14.2	89	58.8	47 to 69		1.43	0.87 to 2.36	.15
Quartiles for time from initial diagnosis to diagnosis of relapse, months				.20			
< 36.4	90	65.1	54 to 74		1.00		
≥ 36.4 to < 43.3	92	63.3	52 to 72		1.09	0.67 to 1.79	.72
≥ 43.3 to < 56.5	90	70.7	59 to 79		0.76	0.45 to 1.29	.31
≥ 56.5	91	73.8	63 to 82		0.66	0.38 to 1.12	.13
Quartiles for time from end of first-line treatment to diagnosis of relapse, months				.30			
< 12.0	91	63.2	52 to 72		1.00		
≥ 12.0 to < 18.9	91	66.2	55 to 75		0.92	0.56 to 1.50	.74
≥ 18.9 to < 32.1	91	69.8	59 to 79		0.74	0.44 to 1.23	.25
≥ 32.1	90	73.5	63 to 82		0.62	0.37 to 1.06	.083
Site of relapse				.73			
Isolated to bone marrow	284	67.5	62 to 73		1.00		
Extramedullary and bone marrow	79	70.7	59 to 79		0.92	0.58 to 1.16	.73
Immunophenotype				.22			
Pro-B ALL	14	64.3	34 to 83		1.00		
Common ALL	251	70.1	64 to 75		0.79	0.32 to 1.95	.61
Pre-B ALL	57	68.4	42 to 68		1.27	0.48 to 3.33	.63
Biphenotypic	7	60.0	13 to 88		0.68	0.13 to 3.51	.65
HSCT				.0012			
No	183	58.9	52 to 66		1.00		
Yes	159	76.3	69 to 82		0.52	0.35 to 0.78	.001
Unknown	21						
Donor for HSCT				.0078			
Matched family	41	89.7	75 to 96		1.00		
Matched unrelated	113	73.0	64 to 80		3.16	1.11 to 8.98	.031
Mismatched	5	80	5 to 75		8.73	1.95 to 39.1	.005
Genetic characteristics of relapses							
ETV6-RUNX1 gene fusion				.012			
Negative	231	64.2	58 to 70		1.00		
Positive	80	79.7	69 to 87		0.51	0.30 to 0.87	.013
BCR-ABL1 gene fusion				.33			
Negative	299	68.4	63 to 73		1.00		
Positive	8	87.5	39 to 98		0.39	0.054 to 2.79	.35

(continued on following page)

TABLE 1. Clinical and Genetic Parameters and Their Association With Outcome (continued)

Parameters	Total No. of Patients	EFS at 10 Years					
		EFS, %	95% CI	*P**	HR	95% CI	*P***
TCF3-PBX1 gene fusion							
Negative	240						
Positive	1	—			—		—
MLL-AF4 gene fusion							
Negative	304						
Positive	2	—			—		—
Other MLL gene fusion				.81			
Negative	260	65.8	59 to 71		1		
Positive	8	62.5	23 to 86		1.15	0.36 to 3.6	.82
P2RY8-CRLF2 gene fusion				.31			
Negative	233	66.2	60 to 72		1		
Positive	8	50.0	15 to 75		1.68	0.61 to 4.6	.31
High hyperdiploidy				.037			
Negative	192	63.9	57 to 70		1		
Positive	51	80.3	66 to 89		0.50	0.26 to 0.97	.041
Low hyperdiploidy				.79			
Negative	228	67.3	61 to 73		1		
Positive	15	66.7	38 to 85		1.13	0.46 to 2.79	.79
Hypodiploidy				.011			
Negative	239	68.0	62 to 74		1		
Positive	4	25.0	9 to 67		4.01	1.25 to 12.8	.019
IKZF1 loss				.51			
No	164	66.9	59 to 74		1		
Yes	79	62.8	51 to 72		1.17	0.74 to 1.83	.51
CDKN2A/B loss				.33			
No	170	64.0	56 to 71		1		
Yes	73	69.4	57 to 79		0.79	0.48 to 1.28	.33
ETV6 loss				.69			
No	173	64.4	57 to 71		1		
Yes	71	68.8	57 to 78		0.90	0.55 to 1.47	.68
PAX5 loss				.96			
No	194	65.6	59 to 72		1		
Yes	49	64.9	50 to 77		1.01	0.59 to 1.72	.96
BTG1 loss				.39			
No	207	66.3	59 to 72		1		
Yes	35	60.0	42 to 74		1.28	0.72 to 2.28	.39
RB1 loss				.68			
No	220	65.1	58 to 71		1		
Yes	22	68.2	45 to 83		0.85	0.39 to 1.84	.68
EBF1 loss				.38			

(continued on following page)

TABLE 1. Clinical and Genetic Parameters and Their Association With Outcome (continued)

Parameters	Total No. of Patients	EFS at 10 Years					
		EFS, %	95% CI	*P**	HR	95% CI	*P***
No	227	66.2	60 to 72		1		
Yes	16	56.3	30 to 76		1.42	0.65 to 3.07	.38
TP53 loss				.0031			
No	222	67.8	62 to 74		1		
Yes	11	36.4	11 to 63		3.07	1.40 to 6.69	.005
TP53 mutation				.015			
No	233	68.3	62 to 74		1		
Yes	12	41.2	15 to 67		2.53	1.16 to 5.51	.019
NRAS mutation				.32			
No	225	65.8	59 to 72		1		
Yes	22	77.3	54 to 90		0.63	0.26 to 1.57	.32
KRAS mutation				.71			
No	234	66.8	60 to 72		1		
Yes	13	68.4	34 to 87		0.83	0.30 to 2.25	.71
FLT3 mutation				.48			
No	198	69.0	62 to 75		1		
Yes	7	57.1	17 to 84		1.52	0.48 to 4.84	.48
TP53 loss and mutation				.0052			
No	225	69.0	62 to 75		1		
Yes	20	45.0	23 to 65		2.42	1.28 to 4.58	.007

Abbreviations: EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; pre-B ALL, pre-B-cell acute lymphoblastic leukemia; pro-B ALL, pro-B-cell acute lymphoblastic leukemia.

*Log-rank test.

**Cox regression.

test. For EFS analysis, subsequent relapse, therapy-related death, secondary malignancies, and patients who did not achieve morphologic remission after 10 weeks of treatment (nonresponse) were considered adverse events. Time to event was estimated from the dates of relapse diagnosis to event. Death before achieving a remission (death as a result of induction treatment) or nonresponse was categorized as event with zero time to event. EFS, OS, CIR, and CID stated in our analyses always correspond to 10-year observation time. Statistical analyses were conducted using SPSS version 23 (SPSS, Chicago, IL), STATA version 14.2 statistical software (STATA, College Station, TX), and R version 3.3.2 for statistical computing. A two-sided P value $< .05$ was considered significant.

RESULTS

Clinical Characteristics

A total of 413 children and adolescents with late bone marrow ALL relapses were enrolled in the study (Fig 1). Median follow-up time was 9.4 years (95% CI, 8.8 to 10.2 years). Overall EFS and OS were 67% (95% CI, 62% to 71%) and 76% (95% CI, 72% to 80%), respectively (Data Supplement). Forty-one patients were excluded from further analyses because of death as a result of induction treatment or lack of MRD data after induction (Fig 1). In the remaining cohort (n = 372), shorter time to relapse was associated with poorer response to induction treatment or nonresponse as the event after relapse (Data Supplement). International trials for treatment of relapses have used different cutoffs defining late relapse at 30 or 36 months after diagnosis to relapse. However, survival in patients who relapsed either between 30 and 36 months after diagnosis or at 36 months or more did not significantly differ in our cohort, supporting that patients relapsing between 30 and 36 months after initial diagnosis are adequately categorized as intermediate risk and not high risk, for patients who received first-line therapy based on the ALL BFM or COALLtrials (Data Supplement). This might not be the same after other first-line therapies.

About half the patients (190 of 372; 51%) responded well (MRD of less than 10^{-3}), whereas 182 patients (49%; MRD $\geq 10^{-3}$) responded poorly to induction treatment (Fig 1). Among patients with available morphology data after induction, 97.5% of patients (363 of 372) had less than 25% leukemic blasts and nine patients had more than 25% leukemic blasts in the bone marrow after induction. EFS was significantly lower in these nine patients (22%; 95% CI, 4% to 51%; Data Supplement). Taken together, late bone marrow ALL relapses occurred over a wide time range after cessation of first-line therapy, and a shorter time to relapse was correlated with poor MRD response to induction and subsequent nonresponse. Even though about half of all patients with late bone marrow BCP-ALL relapses had poor MRD-based responses to induction, EFS was favorable in the entire group.

TABLE 2. Final Multivariable Cox Regression Models for EFS

Response to Induction Treatment	No. of Patients	HR	95% CI	P
Good response				
All				
TP53 loss/mutation				
No	120	1.00		
Yes	12	3.37	1.48 to 7.68	.004
Isolated bone marrow relapses				
TP53 mutation				
Wild-type	86	1.00		
Mutation	6	4.38	1.03 to 7.27	.007
Poor response				
All				
MRD $\geq 10^{-3}$ to $< 10^{-2}$	53	1.00		
MRD $\geq 10^{-2}$	53	2.40	1.23 to 4.65	.010
TP53 loss				
Diploid	102	1.00		
Loss	4	4.51	1.33 to 15.25	.016
Isolated bone marrow relapses				
MRD $\geq 10^{-3}$ to $< 10^{-2}$	69	1.00		
MRD $\geq 10^{-2}$	81	1.96	1.11 to 3.46	.020
All good and poor responders				
MRD $< 10^{-4}$	95	1.00		
MRD $\geq 10^{-4}$ to $< 10^{-3}$	37	1.47	0.76 to 2.83	.26
MRD $\geq 10^{-3}$ to $< 10^{-2}$	57	0.93	0.49 to 1.80	.84
MRD $\geq 10^{-2}$	56	2.33	1.35 to 4.01	.002
TP53 loss/mutation				
No	225	1.00		
Yes	20	2.51	1.32 to 4.78	.005
Isolated bone marrow relapses				
MRD $< 10^{-4}$	85	1.00		
MRD $\geq 10^{-4}$ to $< 10^{-3}$	45	2.06	1.06 to 3.99	.033
MRD $\geq 10^{-3}$ to $< 10^{-2}$	69	1.39	0.72 to 2.70	.33
MRD $\geq 10^{-2}$	81	2.80	1.57 to 5.00	0

NOTE. Cox regression analysis was performed as stepwise forward testing. Models were compared using the log likelihood-ratio test. All variables that reached significance in univariable survival analysis were included: allogeneic hematopoietic stem cell transplantation donor in poor response group; *ETV6-RUNX1*; *BCR-ABL*; high hyperdiploidy; hypodiploidy; and *TP53* mutation, deletion, or both, if both significant. The following are all variables that reached significance in the distribution between minimal residual disease subgroups: time to relapse, *IKZF1* loss, and *CDKN2A* or *CDKN2B* loss.

Abbreviations: EFS, event-free survival; HR, hazard ratio; MRD, minimal residual disease.

Prognostic Subgroups in Good Responders to Induction: Good^{A} (MRD $< 10^{-4}$) Versus Good^{B} (MRD $\geq 10^{-4}$ to $< 10^{-3}$)

In patients who responded well to induction treatment (MRD $< 10^{-3}$), the EFS was 72% (95% CI, 64% to 78%) and the OS was 82% (95% CI, 75% to 87%). To verify 10^{-3} as the best cutoff and evaluate the additional impact of genetic alterations, we performed additional subgroup analyses within finer subdivisions of MRD (Fig 1). The difference between the EFS in the patient subgroup with good^{A} responses to induction and the EFS in the subgroup with good^{B} responses did not reach statistical significance (Fig 2A; 75% *v* 64%; $P = .102$). The CIR was similar in both subgroups, but CID was significantly higher in patients with good^{B} responses (Fig 2B; $P = .024$). Therapy-related deaths were more frequent in patients who received allo-HSCT (2 of 21; 9.5%) than in patients who did not receive allo-HSCT (5 of 154 [3.3%]; $P = .017$), with both patient subgroups containing similar percentages of patients who underwent allo-HSCT (11% *v* 14%; $P = .622$). OS was similar in both patient subgroups (Fig 2C).

The site of relapse modified the effect on survival: in patients with relapses restricted only to the bone marrow, EFS was significantly different between good^{A} and good^{B} responders (79% *v* 61%; $P = .023$), whereas it did not differ in patients with extramedullary plus bone marrow involvement (Data Supplement). Fewer patients with good^{A} response to induction treatment had relapses harboring an *IKZF1* deletion compared with patients with good^{B} responses (Fig 3; 17% *v* 42%; $P = .001$). Within the good^{B} responders with an adverse event, leukemias harboring *IKFZ1* deletions form a cluster, co-occurring with deletions in *PAX5* or *ETV6* or mutations in *BTG1* or *TP53* (Fig 3). *TP53* aberrations were the only adverse parameter independently associated with EFS in multivariable analyses of MRD good responders (Table 2) that included covariates associated with MRD response to induction and survival previously identified in univariable analyses (Table 1; Data Supplement).

Prognostic Subgroups in Poor Responders to Induction: Poor^{A} Response (MRD $\geq 10^{-3}$ to $< 10^{-2}$) Versus Poor^{B} Response (MRD $\geq 10^{-2}$)

Patients who responded poorly to induction treatment (MRD $\geq 10^{-3}$) had EFS of 65% (95% CI, 57% to 71%) and

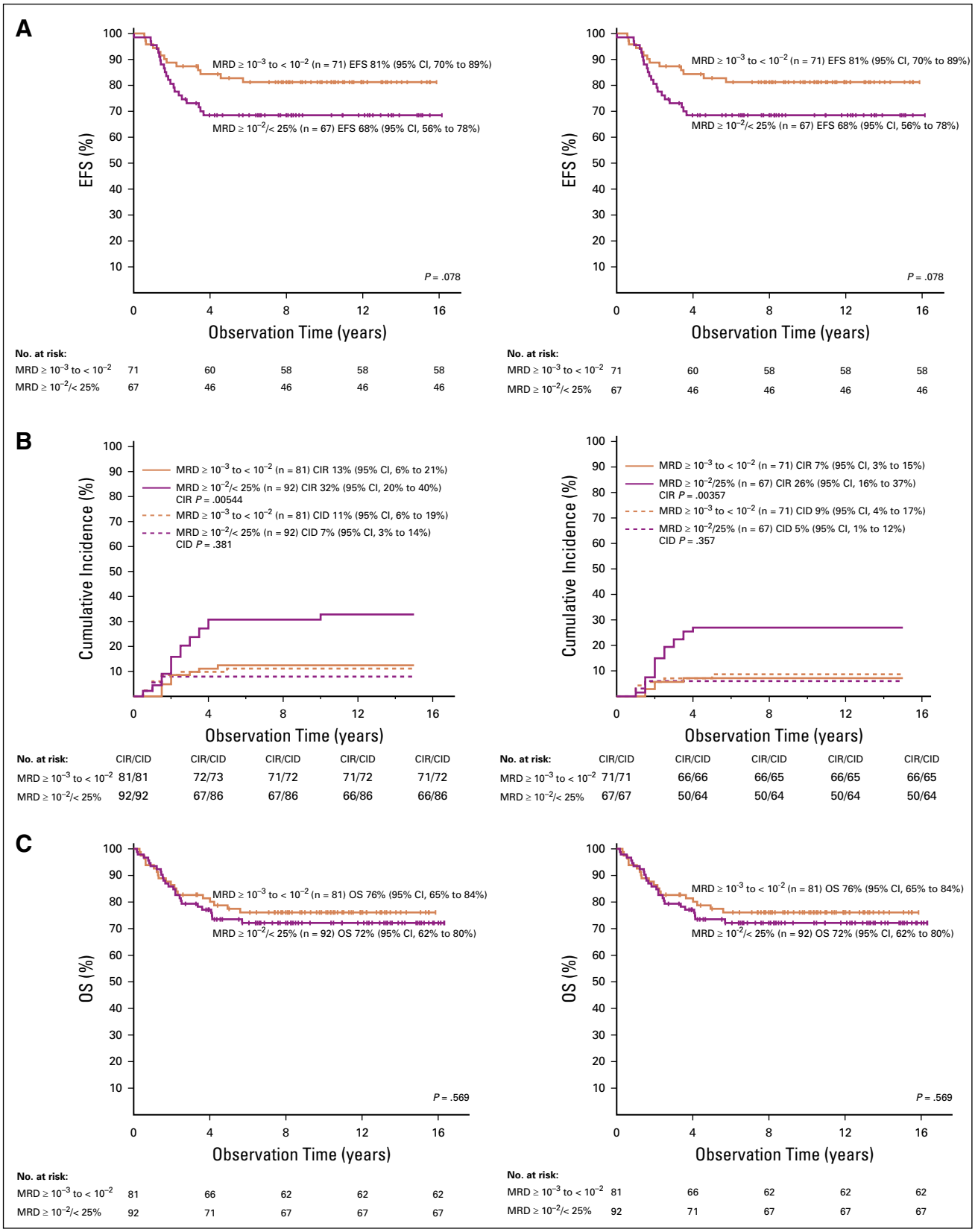

FIG 4. Survival difference between two subgroups of poor responders to induction. The left panel shows the intention to treat (receive allogeneic hematopoietic stem-cell transplantation [allo-HSCT]) analyses and the right panel shows the analyses for patients who received allo-HSCT. (A) Kaplan-Meier analysis comparing the 10-year event-free survival (EFS) in poor responders to induction therapy. (B) Competing (continued on following page)

OS of 74% (95% CI, 67% to 80%). To identify new prognostic response groups and evaluate the additional impact of genetic alterations, subgroup analyses were carried out with finer MRD-based subdivisions of poor response to induction (Fig 1). EFS was significantly superior in patients with poor^{A} response to induction compared with patients with poor^{B} response (Fig 4A; 74% *v* 56%; $P = .02$). This difference in EFS was the result of significantly more subsequent relapses occurring in poor^{B} responders (Fig 4B). OS did not significantly differ between patients with poor^{A} or poor^{B} responses to induction (Fig 4C). Both subgroups of poor responders who received allo-HSCT had favorable outcomes (Fig 4; EFS, 81% *v* 68%; OS, 84% *v* 76%). In contrast, poor responders who did not receive allo-HSCT had very dismal EFS (10%; 95% CI, 3% to 24%) and OS (41%; 95% CI, 23% to 58%), confirming the importance of allo-HSCT for this subgroup. Clinical and genetic characteristics did not significantly vary between poor^{A} and poor^{B} responder subgroups, excepting that relapses more frequently harbored *ETV6-RUNX1* fusions in patients with poor^{A} responses to induction (Fig 3; Data Supplement). Poor^{B} response to induction was an independent prognostic marker in multivariable analysis; however, the final prediction model resulting from our analyses included *TP53* loss as independent predictor of poor outcome as well (Data Supplement). A number of *TP53* mutations were partly overlapping with *TP53* losses, but separately, they did not reach statistical significance. Our results confirm that outcome in patients responding poorly to induction for late bone marrow ALL relapses is improved by intensifying treatment with allo-HSCT. Except for rare *TP53* losses, the panel of genetic markers assessed is not of additional prognostic value.

Impact and Prediction of MRD Levels Before Allo-HSCT

High MRD values directly before HSCT have previously been shown to have prognostic value for patients with ALL.[16] Our trial data included MRD assessment in bone marrow samples collected after induction treatment and 30 days or fewer before allo-HSCT. We verified in our cohort that MRD at 30 days or fewer before allo-HSCT predicted poor survival in patients with late bone marrow ALL relapses; EFS was worse in patients with MRD of 10^{-3} or greater (late nonresponders) compared with patients with MRD of less than 10^{-3} before allo-HSCT (50% *v* 81%; $P = .016$), whereas EFS was remarkably good in patients in whom MRD was reduced to less than 10^{-4} before allo-HSCT (Fig 5A; 84%). Correspondingly, patients with MRD of 10^{-3} or greater before allo-HSCT were 4.9-fold more likely to suffer a subsequent event after allo-HSCT than those with MRD of less than 10^{-4} (Data Supplement). CIR, but not CID, was significantly higher in patients with MRD of 10^{-3} or greater before allo-HSCT than in patients with MRD of less than 10^{-3} (Fig 5B). Ninety-one percent of patients who responded poorly to induction reached MRD levels of less than 10^{-3} before allo-HSCT, and 80% even reached MRD levels of less than 10^{-4} (Fig 5D).

We then investigated the predictive power of MRD assessment after induction treatment for high MRD values immediately before allo-HSCT. The proportion of patients who reached MRD of less than 10^{-3} (83%) or even less than 10^{-4} (59%) before allo-HSCT was significantly lower in the subgroup of patients with MRD of 10^{-2} or greater than in patients with MRD of 10^{-3} or greater to MRD of less than 10^{-2} after induction (Fig 5E; Data Supplement; 96% and 83%, respectively; $P = .037$). Collectively, MRD of 10^{-2} or greater after induction predicted MRD persistence at levels of 10^{-3} or greater and 10^{-4} or greater before allo-HSCT, which was associated with significantly poorer EFS and a higher incidence of relapse after allo-HSCT.

DISCUSSION

Our study assesses the prognostic value of finer MRD-based response groups and genetic alterations in patients with late bone marrow BCP-ALL relapses who were uniformly treated within the ALL-REZ BFM 2002 trial and the subsequent ALL-REZ BFM Registry. In this substantially enlarged cohort with long-term follow-up, we reliably confirm that MRD-based stratification using the established 10^{-3} MRD cutoff produces excellent EFS and OS for patients with late bone marrow relapses.[9]

Generally, the types of agents in induction treatment and their dosages determine the proportion of patients in whom MRD is reduced to below a certain prognostically valuable cutoff level after induction.[2,9,17] Patients in the ALLR3 trial received an anthracycline-based more intensive induction than patients in the ALL-REZ BFM 2002 trial. In that trial, a lower cutoff of 10^{-4} was defined for MRD-based allo-HSCT indication in patients with late bone marrow BCP-ALL relapses.[2,18] It was recently shown in a cohort of 228 patients in the ALLR3 trial that chemotherapy alone produced a favorable outcome in patients with MRD of less than 10^{-4} after induction.[18] Among patients in the ALL-REZ BFM 2002 trial with relapses restricted to only the bone marrow, EFS was significantly lower in the subgroup with MRD from 10^{-4} or greater to less than 10^{-3} (good^{B}) versus MRD of less than 10^{-4} (good^{A}) after induction. So the question arises of whether good^{B} responders would benefit from

FIG 4. (Continued). risk analysis of cumulative incidence of subsequent relapses (CIR) and cumulative incidence of treatment-related deaths (CID) at 10 years in patients who responded poorly to induction therapy. (C) Kaplan-Meier analysis comparing the 10-year overall survival (OS) in poor responders to induction therapy. Minimal residual disease (MRD) in bone marrow was used to more finely divide poor response into two subgroups (MRD $< 10^{-2}$ to $\geq 10^{-3}$ and MRD $\geq 10^{-2}$) after induction therapy.

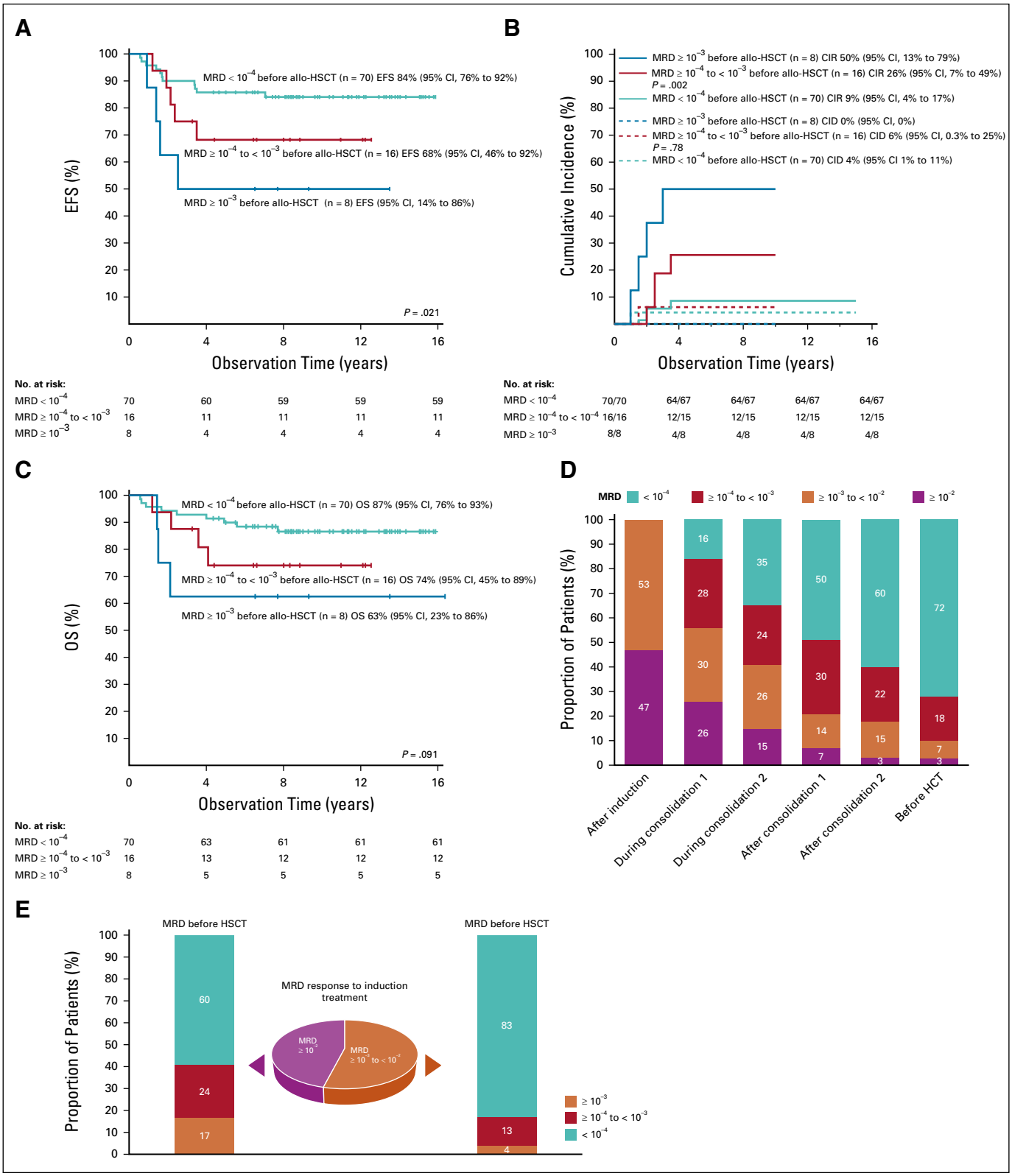

FIG 5. Minimal residual disease (MRD) before allogeneic hematopoietic stem-cell transplantation (allo-HSCT) predicts survival and its kinetics after completion of induction treatment. (A) Kaplan-Meier analysis estimating the 10-year event-free survival (EFS) among patient subgroups grouped according to the level of MRD that was reached immediately before allo-HSCT. (B) The corresponding competing risk analysis of cumulative incidence of subsequent relapses (CIR) and cumulative incidence of treatment-related deaths (CID) at 10 years in the same MRD-based patient subgroups described in panel A. (C) Kaplan-Meier analysis estimating the 10-year overall survival (OS) in the same patient subgroups as in panel A. Only patients (continued on following page)

treatment intensification with allo-HSCT in CR2. The higher proportion of therapy-related deaths among good^{B} responders is partly related to the small number of patients in whom allo-HSCT was performed. We interpret the similar OS between good^{B} and good^{A} responders as a justification to intensify with allo-HSCT only after second relapse rather than assigning all good^{B} responders to receive allo-HSCT within the first relapse treatment by decreasing the MRD-based cutoff to 10^{-4} (Data Supplement). Thus, we do not advise lowering the MRD cutoff for allo-HSCT to 10^{-4} in patients treated according to the ALL-REZ BFM 2002 strategy.

Excellent outcomes (EFS and OS $>$ 80%) were achieved in patients with MRD of 10^{-3} or greater to MRD of less than 10^{-2} after induction treatment who received allo-HSCT in CR2, which has not been observed in other trials[18] and which suggests that there is not an urgent need for additional treatment intensification in these patients. In comparison, patients with MRD of 10^{-2} or greater who received allo-HSCT in CR2 had significantly worse outcomes. The prognostic relevance of MRD before allo-HSCT in our cohort corroborated data reported by Bader et al[16] for intermediate-risk relapses using the 10^{-4} MRD cutoff. MRD persisted at 10^{-4} or greater until before allo-HSCT significantly more frequently in the subgroup with MRD of 10^{-2} or greater than with MRD of 10^{-3} or greater to MRD of less than 10^{-2} after induction. Thus, patients with MRD of 10^{-2} or greater may benefit from novel postinduction treatment approaches, which should be prospectively investigated in future controlled trials. But interestingly, patients with MRD of 10^{-4} or greater and even 10^{-3} or greater before allo-HSCT unexpectedly had a relatively good prognosis after allo-HSCT in our cohort and clearly seem to benefit from an allo-HSCT. Even so, this patient group in our cohort had a particularly poor prognosis. We defined them as late nonresponders and will classify nonresponse as an adverse event in future trials. These late nonresponders would be eligible for prospective phase I/II trials or salvage therapies with drugs having other mechanisms of action before allo-HSCT, such as immunotherapeutics (ie, by targeting CD19), small molecules, or a combination thereof. We identified patients with 25% or more leukemic blasts after induction as the early nonresponder subgroup with the lowest chance to survive. These patients should be removed from the trial directly after induction and enrolled in phase I/II trials or receive individual, potentially targeted, treatment recommendations.

We identified *TP53* alterations (mutations and/or deletions) as the only genetic marker independently associated with poor outcome in the different response groups of late bone marrow ALL relapses. *TP53* mutations resulting in a dysfunctional mutant protein could be directly targeted and functionally restored by the *APR-246* compound, a potentially attractive strategy to pursue in future research.[19-21] Other genetic alterations associated with poor outcome in newly diagnosed or relapsed ALL, such as *IKZF1*$^{+}$,[22] *KRAS* mutations,[14,21] or *IKZF1* or *PAX5* deletions,[18] are either rare in our comparably favorable-risk cohort and thus they are of little prognostic relevance or were not associated with prognosis in our cohort. The only exception here is the presence of hypodiploidy,[13] which mainly overlaps with the occurrence of *TP53* mutations or deletions in our cohort. A more comprehensive genetic characterization using genome-wide technologies, such as RNA sequencing, epigenetic approaches, and high-density single nucleotide polymorphism arrays in large collaborative studies for children with ALL relapses may identify new genetic and epigenetic characteristics predicting response to induction or associated with survival. Ideally, those markers may serve as suitable novel targets for signal transduction inhibitors or immunotherapeutics.[22-24]

We conclude that the ALL-REZ BFM approach for MRD response-adapted allo-HSCT stratification in patients with late bone marrow BCP-ALL relapses is very effective and results in stably improved long-term survival probabilities of more than 70%. New late bone marrow BCP-ALL relapse trials should continue to apply MRD response-based indication for allo-HSCT in CR2 using the established prognostic cutoff according to induction intensity. Prognosis could be further improved by controlled protocol-based treatment intensification in patients with MRD of 10^{-2} or greater after induction and in patients with *TP53* alterations at relapse independently of MRD-based response.

FIG 5. (Continued). who received allo-HSCT are included in the analyses. (D) Each bar shows the proportion of patients assigned to each of the four more finely defined MRD categories. Bars compare the MRD kinetics in patients with bone marrow relapses of B-cell precursor acute lymphoblastic leukemia during treatment at the six indicated sequential bone marrow collection times between completion of induction treatment and 30 days or fewer before allo-HSCT. The following are details for the *x*-axis labels: after induction (after 2 and 4 weeks of treatment); during consolidation 1 (after 6 weeks of treatment); during consolidation 2 (after 9 weeks of treatment); after consolidation treatment 1 (after 11 weeks of treatment); after consolidation treatment 2 (after 13 weeks of treatment); and before allo-HSCT (after 15 weeks of treatment and 30 days or fewer before allo-HSCT). (E) Each bar shows the proportion of patients with the three MRD response levels indicated by color. The two bars compare patients with MRD $\geq 10^{-2}$ (left) and patients with MRD $\geq 10^{-3}$ to $< 10^{-2}$ (right) after induction at the time point 30 days or fewer before allo-HSCT. The pie chart in the center shows the proportion of patients with MRD $\geq 10^{-2}$ (purple) and MRD $\geq 10^{-3}$ to $< 10^{-2}$ (orange) response to induction.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improving Stratification for Children With Late Bone Marrow B-Cell Acute Lymphoblastic Leukemia Relapses With Refined Response Classification and Integration of Genetics

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